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14. ABSTRACT

The purpose of this project is to identify the incidence of post traumatic hypopituitarism (PTH) in mild TBI and develop criteria for assessing which patients with a mild TBI are at risk for developing PTH. This study will also correlate the characteristics of the individuals with PTH by neuropsychological, neurophysiological and imaging testing as they relate to functional outcome. At 6 months post injury, patients will be screened for anterior pituitary function 121 subjects have been recruited as of July 15, 2012; 96 subjects, of which 45 are mTBI, have reached the 6 month point, where data collection (i.e. blood samples) for this project occurs. 20 subjects were found to have hypopituitarism. Further details are in the body of this report

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Introduction: This report outlines Dr. Masel's participation in the Mission Connect Mild Traumatic Brain Injury (mTBI) Translational Research Consortium during the time period of August 1, 2011 through July 31, 2012. Dr. Masel is the PI for Specific Aim 2.3, which is designed to study the diagnosis of post traumatic hypopituitarism after mTBI. The research activities of Specific Aim 2.3 are being conducted in collaboration with three other clinical projects in the Consortium: Specific Aims 2.1 (PI Levin), 2.2 (PI Papanicalaou/McCarthy), and 3.1.2-3.1.7 (PI Robertson) as the Integrated Clinical Protocol (ICP), which will use a shared group of subjects. For the Observational Studies (SA 2.1, 2.2, 2.3), the goal is to enroll 100 mTBI subjects that do not receive study drug (Specific Aim 3.1) and 100 subjects with Orthopedic Injuries (OI) for comparison. This project will use only the mTBI subjects, for whom we will determine the incidence of hypopituitarism following mTBI and develop criteria for assessing which mTBI patients are at high risk for developing posttraumatic hypopituitarism and should have routine post-injury screening. We will also determine the relationship between post-traumatic hypopituitarism and functional outcome, cognitive recovery, and resolution of PCS at six months after mTBI. We will also examine the incidence of single and multiple pituitary hormone deficiencies. The clinical characteristics, MRI imaging results, EEG and MEG results of the subjects who have pituitary deficiency will be compared to those with normal pituitary function. The relationship between pituitary dysfunction and functional outcome, cognitive recovery, and resolution of PCS will be examined.

Body of report

SA #2.3: **To study diagnosis of post-traumatic hypopituitarism after mTBI**
SA #2.3.1: To determine the incidence of hypopituitarism following mTBI.
SA #2.3.2: To develop criteria for assessing which mTBI patients are at high risk for developing posttraumatic hypopituitarism and should have routine post-injury screening.

Relative to SA #2.3.1 and 2.3.2:

As of July 15, 2012, 1,793 potential candidates have been screened for participation in this project. Of these, 1672 were excluded, and 121 have been enrolled, 54 of these (45%) in the past reporting year. For a full discussion of subject screening and recruitment, please refer to Dr. Levin's report.

At the 6 Month Visit, mTBI subjects have blood samples drawn to examine six hormone levels that are indicative of anterior pituitary function, including somatomedin (IGF-1), thyroid stimulating hormone (TSH), thyroxine (Free T4), prolactin, and total cortisol in all subjects. Total testosterone is tested in male subjects, and 17 β-estradiols is tested in females.

A summary of the mean, standard deviation, and ranges of the test results of pituitary function are presented in Table 1 below. The number of subjects falling outside the standard reference range results is also presented.

Table 1: Summary of Pituitary Lab Results

Cortisol							**Out of Range**		
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	15	9.43	3.36	4.2	14.3	0		0	
Male	30	10.42	4.31	2.4	19.8	1	3%	0	
All	45	10.08	4.00	2.4	19.8	1	2%	0	
Estradiols							**Out of Range**		
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	15	76.77	47.90	11.8	186.7	2	13%	2	13%
IGF-1/Somatomedin							**Out of Range**		
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	15	160.77	74.09	62	267				
Male	30	196.00	86.63	65	388		**See Table 2**		
All	45	183.62	83.16	62	388				
Prolactin							**Out of Range**		
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	15	9.34	6.32	4.5	29.7	0		1	7%
Male	30	8.78	4.82	3.3	25.5	0		1	3%
All	45	8.97	5.31	3.3	29.7	0		2	4%
TSH							**Out of Range**		
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	15	1.53	1.89	0.3	8.0	1	7%	1	7%
Male	30	1.65	1.34	0.5	6.2	0		2	7%
All	45	1.61	1.53	0.3	8.0	1	2%	3	7%
Free T4 Thyroxine							**Out of Range**		
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	15	1.01	0.15	0.8	1.3	0		0	

Male	30	0.97	0.14	0.8	1.3	0		0	
All	45	0.99	0.14	0.8	1.3	0		0	
		Free Testosterone						**Out of Range**	
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Male	25	73.31	31.53	107.6	95.7	4	13%	0	
		Total Testosterone						**Out of Range**	
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Male	28	405.14	194.07	106	819	5	17%	0	

At this point we are reporting both Free and Total Testosterone results. We have recently learned that these lab tests are linked in the Memorial Hermann Hospital Lab, meaning that a Total Testosterone must be done in order to then determine the value for Free Testosterone. We were not advised of this linkage or of the additional cost for the Total Test (~$54.00) when we prepared the original study budget in 2008. The combined cost of both tests is $85.00, considerably more than the $31.00 we were advised was the cost of the Free Testosterone. In addition, we have had difficulties in getting the Free Testosterone result. To date, 28 subjects have a result for Total Testosterone, but only 25 have the associated Free level result. To ensure that we have a result and in consultation with Dr. Urban, we have determined that the Total Testosterone value can be used appropriately in their research analyses, instead of the Free result. This should ensure that we have a valid result for all male subjects, and it will decrease lab costs.

A separate table for the out-of-range values for IGF-1 is provided (Table 2 below), since these results are gender and age dependent.

Table 2: IGF-1 Values That Fall Outside Reference Ranges

Standard* Reference Values				**Standard Values**		**TBI Values**	
Age	**Male (ng/ml)**	**n**	**missing**	**Low**	**%**	**Low**	**%**
18-24 years	121-423 ng/mL	11	2	0		1	11%
25-29 years	112-402 ng/mL	5	1	1	25%	1	25%
30-34 years	89-350 ng/mL	5		1	20%	5	100%
35-39 years	77-323 ng/mL	4	2	0		1	50%
40-44 years	70-307 ng/mL	3		0		3	100%
45-49 years	66-296 ng/mL	2	1	0		1	100%
		30	6	2	8%	12	50%

Standard* Reference Values				**Standard Values**		**TBI Values**	
Age	**Female (ng/ml)**	**n**	**missing**	**Low**	**%**	**Low**	**%**
18-24 years	128-488 ng/mL	6	1	1	20%	1	20%
25-29 years	89-397 ng/mL	3		0		2	67%
30-34 years	71-352 ng/mL	0					
35-39 years	63-330 ng/mL	1	1	0		0	
40-44 years	58-318 ng/mL	3		0		3	100%
45-49 years	54-307 ng/mL	2		0		2	100%
		15	2	1	8%	8	62%

The 8 missing IGF-1 results shown in Table 2 are due to:

1. Incorrect IGF test entered by lab personnel – 5
2. Lab tests not done after sample was drawn – 1
3. Lab tests done but result cannot be located – 2

The lab order sheet for the 6 Month Visit has been revised to increase the accuracy of test entry by the lab personnel, and we are monitoring this very closely. The Research Team meets regularly with the CRU staff to ensure that they are familiar with all aspects of the protocol, and we have increased this interaction as well. To put this in perspective, the mTBI subjects get 6 lab tests for pituitary function at the 6 Month Visit. For the 45 enrolled mTBIs that have completed the 6 Month Visit, this would be a total of 270 tests. The 8 errors in this group represent 3% of the tests done.

Table 2 indicates two parameters used to determine IGF-1 deficiency. The first (labeled: "Standard Values") are the age/gender specific values used by Quest Diagnostics, the outside lab that does the IGF-1 test for Memorial Hermann Hospital-Texas Medical Center However, IGF-I is a very rough estimate of the GH status of an individual and GH provocative stimulation testing, such as with the glucagon stimulation test (GST) is the only way to make a definitive diagnosis of growth hormone deficiency. The normal ranges for IGF-I are difficult to interpret, especially in individuals with TBIs because IGF-I can be influenced by many different variables. Therefore, many subjects who are GH deficient will have IGF-I levels in the normal range. The cutoff of an IGF-I of less than 175 (labeled "TBI Values") is based on our study that correlated the response of the GST with the baseline IGF-I. Zgaljardic, et al. (2011) Serum IGF-1 concentrations in a sample of patients with traumatic brain injury as a diagnostic marker of growth hormone secretory response to glucagon stimulation testing, *Clinical Endocrinology* 74, 365–369

Key research accomplishments

- 45 mTBI subjects (30 male, 15 female) have completed their 6 Month Visit and provided blood samples for this analysis.

- Operational problems with processing these samples have been identified and addressed. No incorrect tests have been order since November 2011, and we have devised a process with the Memorial Hermann Hospital-Texas Medical Center to ensure that lab results are available after processing.

- Dr. Masel has been an active participant in the Clinical Working Group as well as at the Partnering PI Quarterly meetings. He was also invited to attend the 27th Army Science Conference in Orlando, November, 2010.

Dr. Masel was an author on the following paper on the topic of post traumatic hypopituitarism in the past year:
Manifesto for the Current Understanding and management of Traumatic Brain Injury-induced Hypopituitarism. J. Endocrinol. Invest.34:541-543, 2011.

Reportable outcomes

- A preliminary analysis of pituitary hormone showed that of the subjects tested using the "TBI values" for IGF-1Four subjects had two hormonal deficiencies
- Twenty subjects had one hormonal deficiency
- IGF-1 deficiency was the most common finding
- Pituitary deficiencies are common following a mTBI

The following poster was presented at the annual Endocrine society meeting in Houston, June 23-26 on post traumatic hypopituitarism. This poster used data from the Mission Connect mTBI Translational Research Consortium study and acknowledged the DoD Award.

Do Patients with Mild Traumatic Brain Injury Have an Increased Risk for Hypopituitarism?
Authors: Saadia Alvi, Sara Ahmadi, Charles R Gilkison, Randall J Urban, Brent Masel

Conclusion

In Year 4 of this project, enough mTBI subjects have completed their 6 Month Visit to provide preliminary data for analysis. We have found that post traumatic hypopituitarism for single and multiple deficiencies is prevalent at the 6 month time point following a mTBI. A low IGF-1 (an indicator of low growth hormone levels) is the most common hormonal deficiency. At present, there are no published studies on the incidence or prevalence of pituitary dysfunction following mTBI. There are also no hormonal replacement studies in the literature for mTBI. We believe that this project can make a significant contribution in this area.

As noted previously, the IGF-1 level is a crude indicator of the growth hormone level. As low IGF-1 levels are the most common hormonal abnormality in this study, there is a clear need for stimulation testing which will provide a definitive diagnosis. A treatment trial of hormone replacement is also indicated. If indeed the subjects improve symptomatically, this would suggest a role of hormonal replacement for the treatment of mTBI.

References

Zgaljardic, et al. (2011) Serum IGF-1 concentrations in a sample of patients with traumatic brain injury as a diagnostic marker of growth hormone secretory response to glucagon stimulation testing, *Clinical Endocrinology* 74, 365–369

Appendices (Double click on page to open up complete article)

Clinical Endocrinology (2011) 74, 365–369 doi: 10.1111/j.1365-2265.2010.03935.x

ORIGINAL ARTICLE

Serum IGF-1 concentrations in a sample of patients with traumatic brain injury as a diagnostic marker of growth hormone secretory response to glucagon stimulation testing

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Summary

Objective The diagnosis of growth hormone deficiency (GHD) in adults is established through growth hormone (GH) stimulation testing, which is often complex, expensive, time-consuming and may be associated with adverse side effects. The decision to perform GH provocative testing is influenced by clinical findings, medical history and biochemical evidence. We report in this study our experience using the glucagon stimulation test (GST) in assessing GHD in adult patients with traumatic brain injury (TBI) as it relates to baseline serum insulin-like growth factor-1 (IGF-1) concentrations.

Design A receiver operating characteristic (ROC) curve analysis was performed to determine the optimal IGF-1 cut-off for diagnosis of GHD at different potential diagnostic GST cut-off values (<3, <5, & <10 μg/l).

Patients One hundred and thirty-eight patients (98 men and 40 women) with a documented history of moderate to severe TBI were assessed for GHD using serum IGF-1 concentrations and the GST.

Measurements IGF-1 values were compared with peak GH values obtained following the GST.

Results An IGF-1 cut-off value of 175 μg/l minimized the misclassification of GHD patients and GH-sufficient patients and provided a sensitivity of 83% and specificity of 40%, as well as a negative predictive power of 90% considering a criterion for peak GH response of <3 μg/l.

Conclusions Our current findings are consistent with previous work assessing peak GH response using the insulin tolerance test (ITT) in a non-TBI sample, suggesting that diagnostic accuracy may be optimized if the GST is used when obtained serum IGF-1 concentrations are below 175 μg/l. While the decision to perform provocative testing to assess GHD in adult patients should be based on the clinician's clinical impression, the findings from this retrospective study can provide useful clinical information and serve as a guide.

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Introduction

Recent work has demonstrated that hypopituitarism, particularly growth hormone deficiency (GHD), is common among survivors of traumatic brain injury (TBI).[1] Prevalence of GHD in patients with TBI varies from 10% to 25%.[2] GHD is associated with multiple physical, metabolic and neuropsychological manifestations including, but not limited to, diminished lean body mass, disrupted lipoprotein and carbohydrate metabolism, reduced bone mineral density and impaired cardiac function, as well as declines in cognitive functioning, fatigue, and diminished quality of life.[3,4] Therefore, providing appropriate diagnosis of GHD in patients with the aforementioned symptoms is crucial, as subsequent management using growth hormone (GH) replacement therapy in GHD patients with and without TBI has been shown to be beneficial.[4–7]

The diagnosis of GHD is established by use of provocative testing. The maximum or peak GH secretion following provocative testing (e.g. insulin) is used as a surrogate of the capacity of the pituitary to release GH. Currently, several types of provocative tests are being used to diagnose GHD of which the insulin tolerance test (ITT) has been considered the 'gold standard'.[8–10] However, the use of ITT is limited by low patient tolerance (e.g. discomfort), labour intensiveness and potential risks (e.g. hypoglycaemia). Furthermore, ITT is contraindicated in patients with electrocardiographic evidence of ischaemic heart disease or in patients with seizure disorders.[11,12] The latter is common